DRUGS USED TO SUPPRESS INFLAMMATORY AND IMMUNE REACTIONS

The main anti-inflammatory agents are the **glucocorticoids** and the **nonsteroidal anti-inflammatory drugs**. The glucocorticoids are dealt with in detail in Chapter 20 and their immunosuppressive actions are discussed briefly at the end of this chapter; the nonsteroidal anti-inflammatory drugs (NSAIDs) are dealt with below. Other drugs considered in this chapter are the **antirheumatoid agents**, drugs used to treat gout and the **immunosuppressants**. At the end of the chapter, brief consideration is given to potential new developments in the general area of drugs used to suppress inflammatory and immune reactions.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

Non-steroidal anti-inflammatory drugs are among the most widely used of all therapeutic agents. Some important examples are listed in Table 12.1. They are frequently prescribed for 'rheumatic' musculoskeletal complaints; it is estimated that more than 20 million people in the United Kingdom experience this type of disorder and 8 million of these consult their doctors in the course of a year, constituting 23% of all consultations. In the USA upwards of 7 million prescriptions for NSAIDs are written each year. In addition, very large quantities of these drugs are bought over the pharmacist's counter by the general public, without prescription, for treatment of headache, toothache and a variety of other minor complaints. It is probable that most bathroom medicine cupboards in the UK harbour a bottle containing aspirin or paracetamol or some other NSAID.

There are now more than 50 different NSAIDs on the market and there is a continuing flow of new preparations. The fact that so many new compounds have been produced and are still being produced is a reflection of the fact that none is ideal in controlling or modifying the signs and symptoms of inflammation, particularly in the common inflammatory joint diseases. A particular problem is that virtually all NSAIDs can have significant unwanted effects, especially in the elderly.

PHARMACOLOGICAL ACTIONS

NSAIDs include a variety of different agents of different chemical classes. Most of these drugs

Table 12.1 Comparison of some commonly used NSAIDs

Drug	Plasma $t_{\frac{1}{2}}$ (hours)	Action: Analg	Action: Antipyr	Action: Anti-infl	Comments
Salicylic acids					
Aspirin	3–5	+	+	+	Fairly marked GIT upsets and haemorrhage. Tinnitus. Hypersensitivity reactions. Cheap and effective. A drug of first choice for mild analgesia. An encephalitis can be precipitated in children with viral infections.
Diflunisal	8–13	+	−	+	10 times more potent in anti-inflammatory and analgesic effect than aspirin but only 1.5 times more potent in antipyresis. Less GIT irritation than aspirin.
Benorylate		+	+	+	Aspirin–paracetamol ester; broken down in GIT; less GIT irritation than with aspirin.
Propionic acids					All have very similar actions and side effects. Metabolised in liver. Effective and better tolerated than most other NSAIDs. As inhibitors of cyclo-oxygenase naproxen is 20 times more potent than aspirin, the others are equipotent. Ibuprofen is a drug of first choice for inflammatory joint disease because it has the lowest incidence of unwanted effects. Fenbufen is a pro-drug, activated in the liver; less likely to cause bleeding in GIT.
Naproxen	13	+	+	+	
Ibuprofen	2	+	+	+	
Flurbiprofen	4	+	+	+	
Fenbufen	10	+	+	−	
Ketoprofen	2	+	+	+	
Acetic acids					
Indomethacin	2	+	+	+ +	One of the most potent inhibitors of cyclo-oxygenase in vitro. Clinically effective but high incidence of side effects. Headache, dizziness and GIT upsets common.
Sulindac	7 (18)*	+	+	+	A pro-drug manifesting reversible activation, i.e. inter-convertible with its active sulphide metabolite; long duration of action. Enterohepatic cycling. About half the potency of indomethacin.
Fenamates					
Meclofenamic acid	2	+	+	+	Moderate anti-inflammatory actions. GIT upsets. Diarrhoea likely. Haemolytic anaemia has been reported.
Mefenamic acid	4	+	+	±	
Oxicams					
Piroxicam	45	+	+	+ +	Piroxicam is used world-wide for chronic inflammatory conditions. GIT irritation in 20% patients. Tinnitus. Rashes. Metabolised in the liver. Is given once daily. Multiple peaks in plasma suggest enterohepatic recycling. No accumulation in the elderly or in patients with renal impairment.
Tenoxicam	42–98	+	+	+ +	Long $t_{\frac{1}{2}}$ means steady-state plasma concentration only after 2 weeks. Marginally less toxic than piroxicam.
Pyrazolones					
Phenylbutazone	50–100	±	+	+ +	Very potent. More toxic than other NSAIDs. In UK use restricted to ankylosing spondylitis.
Azapropazone	20	+	+	+	Moderate efficacy. Mild GIT irritation.
Paracetamol	2–4	+	+	−	Safe and effective mild analgesic in therapeutic doses; less analgesic efficacy in inflammatory conditions. Chronic use can cause kidney damage. Overdose causes serious hepatotoxicity.
Tolmetin	1	+	+	+	Rapidly absorbed. Excreted in urine within 24 hours. Fairly high incidence of side effects.

*Half-life of active metabolite

Analg = analgesic; Antipyr = antipyretic; Anti-infl = anti-inflammatory; GIT = gastrointestinal tract

See text for details of unwanted effects (p. 287)

have three major types of effect:

- *antipyretic effect*: lowering a raised temperature
- *analgesic effect*: reduction of certain sorts of pain
- *anti-inflammatory effects*: modification of the inflammatory reaction.

In general, all of these effects are related to the primary action of the drugs—inhibition of arachidonate cyclo-oxygenase and thus inhibition of the production of prostaglandins and thromboxanes. However, some aspects of the action of individual drugs may occur by a different mechanism.

Not all NSAIDs manifest the three actions mentioned to the same extent. Most are analgesic, but the degree of anti-inflammatory activity varies: some (such as **aspirin** and **indomethacin**) are strongly anti-inflammatory, some (such as **naproxen, meclofenamate** and **fenclofenac**) are moderately anti-inflammatory, while some (such as **paracetamol**) have essentially no anti-inflammatory activity at all.

In addition to these three categories of action, one of the NSAIDs, aspirin, has particularly pronounced actions on platelets and a significant role in preventing recurrence of myocardial infarction (Ch. 16).

The main pharmacological actions and the common side effects of this group of drugs are outlined below, followed by a more detailed coverage of the salicylates and paracetamol and finally the clinical applications of the group as a whole. A comparison of some aspects of the pharmacology of some commonly used NSAIDs is given in Table 12.1 and the structures of representative agents of each class is given in Figure 12.1.

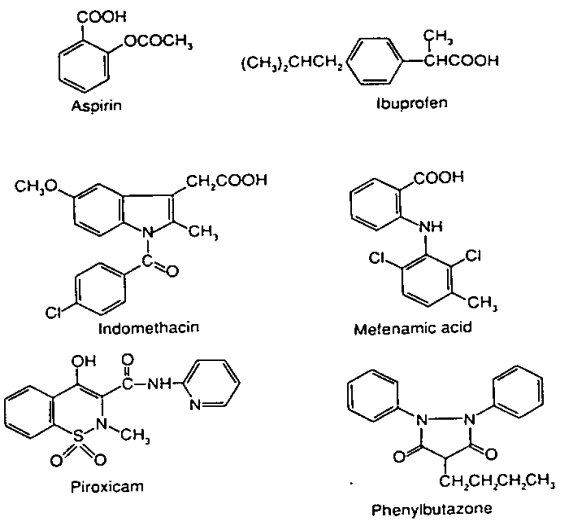

Fig. 12.1 Structures of some representative nonsteroidal anti-inflammatory drugs.

Antipyretic effect

Normal body temperature is regulated by a centre in the hypothalamus and involves a sensitive control of the balance between heat loss and heat production. Fever occurs when there is a disturbance of this hypothalamic 'thermostat', leading to the set-point of body temperature being raised. During an inflammatory reaction, bacterial endotoxins cause the release from macrophages of a pyrogen, which is probably interleukin-1 (IL-1) (Ch. 11). There is some evidence that this pyrogen causes the generation in the hypothalamus of prostaglandins of the E series and that these cause the elevation of the set-point for temperature. If this is so, the action of the NSAIDs in promoting a return to the normal set-point for temperature could be explained as being due to their inhibition of prostaglandin synthesis. Once there has been a return to the normal set-point, the temperature-regulating mechanisms (dilatation of superficial blood vessels, sweating, etc.) then operate to reduce temperature. Normal temperature is not affected by NSAIDs. (For a discussion of this topic see Rainsford 1984.)

Analgesic effect

As explained in Chapter 11 and Chapter 29, several prostaglandins sensitise nociceptive

Unwanted effects

With therapeutic doses, side effects are few and uncommon, though allergic skin reactions sometimes occur. Regular intake over a long period is thought to increase the risk of kidney damage (see p. 288).

Toxic doses (i.e. 2–3 times the maximum therapeutic dose) cause a serious, potentially fatal hepatotoxicity. Renal toxicity is also reported. These toxic effects occur when the liver enzymes catalysing the normal conjugation reactions are saturated, causing the drug to be metabolised by the mixed function oxidases (reactions 3 and 4 in Fig. 12.3). The resulting toxic metabolite, N-acetyl-p-benzoquinone is inactivated by conjugation with glutathione (reaction 5 in Fig. 12.3), but when glutathione is depleted the toxic intermediate accumulates and reacts with nucleophilic constituents in the cell. This causes necrosis in the liver and also in the kidney tubules (reaction 6 in Fig. 12.3).

The initial symptoms of acute paracetamol poisoning are nausea and vomiting, the hepatotoxicity being a delayed manifestation that occurs 24–48 hours later. Treatment entails gastric lavage followed by oral activated charcoal. Further details of the toxic effects of paracetamol are given in Chapter 40. If the patient is seen sufficiently soon after ingestion, the liver damage can be prevented by giving the following:

- agents that increase glutathione formation in the liver (e.g. **acetylcysteine**, which can be given orally or intravenously)
- agents that increase the conjugation reactions (**methionine**, **cysteamine**).

The time since the taking of the drug and the plasma paracetamol concentration are the main guides as to whether the above agents should be given, bearing in mind that if more than 12 hours have passed since the ingestion of a large dose, the antidotes are not likely to be useful and may even make the situation worse, since these compounds have been reported to precipitate hepatic coma.

Paracetamol

- Has analgesic, antipyretic but not anti-inflammatory actions.
- For mechanism of action, see p. 286.
- It is given orally and metabolised in liver ($t_{\frac{1}{2}}$ = 2–4 h).
- Toxic doses cause nausea and vomiting, then after 24–48 h potentially fatal liver damage by saturating normal conjugating enzymes causing the drug to be converted by mixed function oxidases to N-acetyl-p-benzoquinone. This, if not inactivated by conjugation with glutathione, reacts with cell proteins and kills the cell.
- Agents which increase glutathione (acetylcysteine orally or i.v.) or which increase conjugation reactions (e.g. methionine) can prevent liver damage if given early.

Benorylate is an aspirin-paracetamol ester. After metabolism in the liver it releases both active constituents. There is less gastrointestinal disturbance and blood loss than with aspirin itself and as it is more slowly absorbed than paracetamol, overdosage may not cause as much hepatotoxicity. But note that there is an increased risk of kidney damage with combinations of paracetamol and aspirin.

CLINICAL USES OF THE NSAIDs

There is substantial individual variation in clinical response to NSAIDs and considerable unpredictable patient preference for one drug rather than another.

For analgesia

Most NSAIDs have analgesic actions; the types of pain for which they are effective are outlined in the section on pharmacological actions above. Single doses of **aspirin** (approx 600 mg) usually start to have an effect within a few minutes and reach peak action after 1–2 hours. The effect wears off after about 6 hours. Tolerance does not develop and subsequent